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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Kahn et al.

Examiner: Not Assigned

Group Art Unit: Not Assigned

For: REVERSE-TURN MIMETICS AND
METHOD RELATING THERETO

Serial No.: Not Assigned

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Commissioner for Patents
Washington, D.C. 20231

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Mailed in Menlo Park, CA on: October 12, 2001

Dear Sir:

1. Transmitted herewith for filing is the above-identified patent application, including:

Papers required for a filing date under 37 CFR § 1.53(b);
 24 Pages in the specification including:
 19 pages of Description; 4 pages of Claims; 1 page of Abstract;
 Sheets of drawings informal formal;
 X Declaration and Power of Attorney (Unsigned);
 X Applicant is a Small Entity
 Assignment and Recordation Cover Sheet (PTO-1595);
 Information Disclosure Statement and PTO-1449 Form;
 X One (1) Return Receipt Postcard.

2. Publication: APPLICANT HEREBY REQUESTS THAT THE APPLICATION IS NOT PUBLISHED UNDER 35 USC 122(b), and certifies that the invention disclosed in the application has not been and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

3. Filing Fee Calculation

Description	Fee	Claims	Drawings	Tables	Fee
Code					
Basic Fee	201				\$355
Independent Claims	202	1 - 3=	0 x	\$42=	\$ 0
Total Claims	203	9 - 20=	0 x	\$9=	\$ 0
Multiple Dependent Claim	204	2=	2 x	\$140=	\$280
		Total Fees Due		\$635	

4. Payment of Fees

Payment of the filing fee and submission of an executed declaration are deferred.

5. Assignee: CHOONGWAE PHARMA CORPORATION

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REVERSE-TURN MIMETICS AND METHOD RELATING THERETO

TECHNICAL FIELD

The present invention relates generally to reverse-turn mimetic structures and to a chemical library relating thereto.

BACKGROUND OF THE INVENTION

Random screening of molecules for possible activity as therapeutic agents has occurred for many years and resulted in a number of important drug discoveries. While advances in molecular biology and computational chemistry have led to increased interest in what has been termed "rational drug design," such techniques have not proven as fast or reliable as initially predicted. Thus, in recent years there has been a renewed interest and return to random drug screening. To this end, particular strides having been made in new technologies based on the development of combinatorial chemistry libraries, and the screening of such libraries in search for biologically active members.

In general, combinatorial chemistry libraries are simply a collection of molecules. Such libraries vary by the chemical species within the library, as well as the methods employed to both generate the library members and identify which members interact with biological targets of interest. While this field is still young, methods for generating and screening libraries have already become quite diverse and sophisticated. For example, a recent review of various combinatorial chemical libraries has identified a number of such techniques (Dolle, *J. Com. Chem.*, 2(3): 383-433, 2000), including the use of both tagged and untagged library members (Janda, *Proc. Natl. Acad. Sci. USA* 91:10779-10785, 1994).

Initially, combinatorial chemistry libraries were generally limited to members of peptide or nucleotide origin. To this end, the techniques of Houghten et al. illustrate an example of what is termed a "dual-defined iterative" method to assemble soluble combinatorial peptide libraries via split synthesis techniques (*Nature (London)* 354:84-86, 1991; *Biotechniques* 13:412-421, 1992; *Bioorg. Med. Chem. Lett.* 3:405-412, 1993). By this technique, soluble peptide libraries containing tens of millions of members have been obtained. Such libraries have been shown to be effective in the identification of

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opioid peptides, such as methionine- and leucine-enkephalin (Dooley and Houghten, *Life Sci.* 52, 1509-1517, 1993), and a N-acylated peptide library has been used to identify acetalins, which are potent opioid antagonists (Dooley et al., *Proc. Natl. Acad. Sci. USA* 90:10811-10815, 1993). More recently, an all D-amino acid opioid peptide library has been constructed and screened for analgesic activity against the mu ("μ") opioid receptor (Dooley et al, *Science* 266:2019-2022, 1994).

While combinatorial libraries containing members of peptide and nucleotide origin are of significant value, there is still a need in the art for libraries containing members of different origin. For example, traditional peptide libraries to a large extent merely vary the amino acid sequence to generate library members. While it is well recognized that the secondary structures of peptides are important to biological activity, such peptide libraries do not impart a constrained secondary structure to its library members.

To this end, some researchers have cyclized peptides with disulfide bridges in an attempt to provide a more constrained secondary structure (Tumelty et al., *J. Chem. Soc.* 1067-68, 1994; Eichler et al., *Peptide Res.* 7:300-306, 1994). However, such cyclized peptides are generally still quite flexible and are poorly bioavailable, and thus have met with only limited success.

More recently, non-peptide compounds have been developed which more closely mimic the secondary structure of reverse-turns found in biologically active proteins or peptides. For example, U.S. Pat. No. 5,440,013 to Kahn and published PCT WO94/03494, PCT WO01/00210A1, and PCT WO01/16135A2 to Kahn these disclose conformationally constrained, non-peptidic compounds, which mimic the three-dimensional structure of reverse-turns.

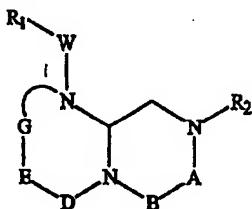
While significant advances have been made in the synthesis and identification of conformationally constrained, reverse-turn mimetics, there remains a need in the art for small molecules, which mimic the secondary structure of peptides. There has been also a need in the art for libraries containing such members, as well as techniques for synthesizing and screening the library members against targets of interest, particularly biological targets, to identify bioactive library members. For example U.S. Pat. No. 5,929,237 and its continuation-in-part U.S. Pat. No. 6,013,458 to Kahn also discloses conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins.

The present invention also fulfills these needs, and provides further related advantages by providing conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins.

SUMMARY OF THE INVENTION

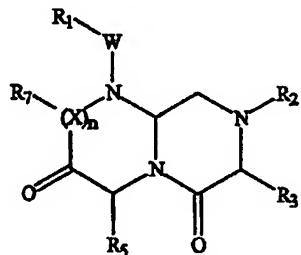
In brief, the present invention is directed to another type of conformationally constrained compounds, which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins. This invention also discloses libraries containing such compounds, as well as the synthesis and screening thereof.

The compounds of the present invention have the following general structure (I):



wherein A is $-(CH_2)-$ or $-(C=O)-$, B is $-(CH_2)-$ or $-(C=O)-$, D is $-(CH_2)-$ or $-(C=O)-$, E is $-(ZR_3)-$ or $-(C=O)-$, G is $-(XR_7)_n$, $-(CH_2)_n(NR_6)-$, $-(C=O)-(XR_7)_n$, or $-(C=O)-$, W is $-Y(C=O)-$, $-(C=O)NH-$, $-(SO_2)-$ or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

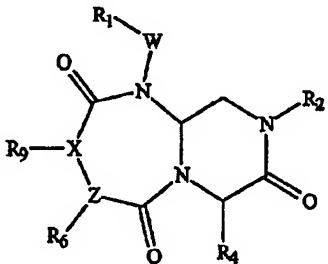
In the embodiment wherein A is $-(CH_2)-$, B is $-(C=O)-$, D is $-(CH_2)-$, E is $-(C=O)-$, and G is $-(XR_7)_n$, the compounds of this invention have the following structure (I'):



Wherein W, Y and n are as defined above, and R₁, R₂, R₃, R₄ and R₇ are as defined in the

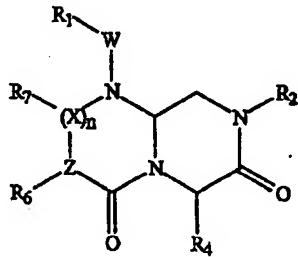
following detailed description.

In the embodiment wherein A is $-(C=O)-$, B is $-(CHR_4)-$, D is $-(C=O)-$, E is $-(ZR_3)-$, and G is $-(C=O)-(XR_3)-$, the compounds of this invention have the following structure (I'):



wherein W, Y and n are as defined above, Z is nitrogen or CH (when Z is CH, then X is nitrogen), and R₁, R₂, R₄, R₆ and R₉ are as defined in the following detailed description.

In the embodiment wherein A is $-(C=O)-$, B is $-(CHR_4)-$, D is $-(C=O)-$, E is $-(ZR_3)-$, and G is $(XR_3)_n-$, the compounds of this invention have the following general structure (I''):



wherein W, Y and n are as defined above, Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero), and R₁, R₂, R₄, R₆ and R₉ are as defined in the following detailed description.

The present invention is also directed to libraries containing compounds of structure (I) above, as well as methods for synthesizing such libraries and methods for screening the same to identify biologically active compounds. Compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier or diluent are also disclosed.

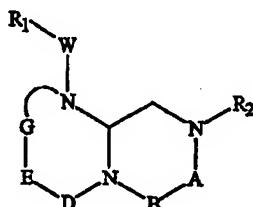
These and other aspects of this invention will be apparent upon reference to the attached figures and following detailed description. To this end, various references are set forth herein, which describe in more detail certain procedures, compounds and/or

compositions, and are incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biological peptide and proteins (also referred to herein as "reverse-turn mimetics" and chemical libraries relating thereto. The reverse-turn mimetic structures of the present invention are useful as bioactive agents, including (but not limited to) use as diagnostic, prophylactic and/or therapeutic agents. The reverse-turn mimetic structure libraries of this invention are useful in the identification of such bioactive agents. In the practice of the present invention, the libraries may contain from tens to hundreds to thousands (or greater) of individual reverse-turn structures (also referred to herein as "members").

In one aspect of the present invention, a reverse-turn mimetic structure is disclosed having the following structure (M):



wherein A is $-(\text{CHR}_3)-$ or $-(\text{C}=\text{O})-$, B is $-(\text{CHR}_4)-$ or $-(\text{C}=\text{O})-$, D is $-(\text{CHR}_5)-$ or $-(\text{C}=\text{O})-$, E is $-(\text{ZR}_6)-$ or $-(\text{C}=\text{O})-$, G is $-(\text{XR}_7)_n-$, $-(\text{CHR}_7)_n(\text{NR}_8)_n-$, $-(\text{C}=\text{O})(\text{XR}_7)_n-$, or $-(\text{C}=\text{O})-$, W is $-\text{Y}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NH}-$, $-(\text{SO}_3)-$ or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

More specifically, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from the group consisting of aminoC₂-alkyl, guanidinoC₂-alkyl, C₁-alkylguanidinoC₂-alkyl, diC₁-alkylguanidino-C₂-alkyl, amidinoC₂-alkyl, C₁-alkylamidinoC₂-alkyl, diC₁-alkylamidinoC₂-alkyl, C₁-alkoxy, Phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C₁-alkylamino, C₁-dialkylamino, halogen, perfluoro C₄-alkyl, C₄-alkyl, C₁-alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl).

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benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridyl, substituted pyridyl, (where the substituents are independently selected from one or more of amino amidino, guanidino, hydrazino, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridyl C_{1-4} alkyl, substituted pyridyl C_{1-4} alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyrimidyl C_{1-4} alkyl, substituted pyrimidyl C_{1-4} alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy or nitro, carboxy, cyano, sulfuryl, or hydroxyl), triazin-2-yl- C_{1-4} alkyl, substituted triazin-2-yl- C_{1-4} alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazol-1-yl- C_{1-4} alkyl, substituted imidazol-1-yl- C_{1-4} alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazone, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazolimyl C_{1-4} alkyl, N-amidinopiperazinyl- $N-C_{0-4}$ alkyl, hydroxy C_{2-5} alkyl, C_{1-5} alkylamino C_{2-5} alkyl, hydroxy C_{2-5} alkyl, C_{1-5} alkylamino C_{2-5} alkyl, C_{1-5} dialkylamino C_{2-5} alkyl, N-amidinopiperidinyl C_{1-4} alkyl and 4-aminocyclohexyl C_{0-4} alkyl.

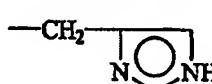
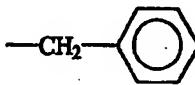
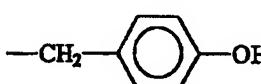
In one embodiment, R_1 , R_2 , R_6 of E, and R_7 , R_8 and R_9 of G are the same or different and represent the remainder of the compound, and R_3 of A, R_4 of B or R_5 of D is selected from an amino acid side chain moiety or derivative thereof. As used herein, the term "remainder of the compound" means any moiety, agent, compound, support,

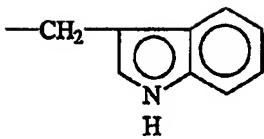
molecule, linker, amino acid, peptide or protein covalently attached to the reverse-turn mimetic structure at R₁, R₂, R₃, R₅, R₇, R₈ and/or R₉ positions. This term also includes amino acid side chain moieties and derivatives thereof.

As used herein, the term "amino acid side chain moiety" represents any amino acid side chain moiety present in naturally occurring proteins including (but not limited to) the naturally occurring amino acid side chain moieties identified in Table 1. Other naturally occurring amino acid side chain moieties of this invention include (but are not limited to) the side chain moieties of 3,5-dibromotyrosine, 3,5-diiodotyrosine, hydroxylsine, γ -carboxyglutamate, phosphotyrosine and phosphoserine. In addition, glycosylated amino acid side chains may also be used in the practice of this invention, including (but not limited to) glycosylated threonine, serine and asparagine.

TABLE 1

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Amino Acid Side Chain Moieties	
Amino Acid Side Chain Moiety	Amino Acid
-H	Glycine
-CH ₃	Alanine
-CH(CH ₃) ₂	Valine
-CH ₂ CH(CH ₃) ₂	Leucine
-CH(CH ₃)CH ₂ CH ₃	Isoleucine
- (CH ₂) ₄ NH ₃ ⁺	Lysine
- (CH ₂) ₃ NHC(NH ₂)NH ₂ ⁺	Arginine
	Histidine
-CH ₂ COO ⁻	Aspartic acid
-CH ₂ CH ₂ COO ⁻	Glutamic acid
-CH ₂ CONH ₂	Asparagine
-CH ₂ CH ₂ CONH ₂	Glutamine
	Phenylalanine
	Tyrosine

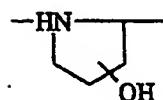


Tryptophan

-CH ₂ SH	Cysteine
-CH ₂ CH ₂ SCH ₃	Methionine
-CH ₂ OH	Serine
-CH(OH)CH ₃	Threonine



Proline



Hydroxyproline

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In addition to naturally occurring amino acid side chain moieties, the amino acid side chain moieties of the present invention also include various derivatives thereof. As used herein, a "derivative" of an amino acid side chain moiety includes modifications and/or variations to naturally occurring amino acid side chain moieties. For example, the amino acid side chain moieties of alanine, valine, leucine, isoleucine and phenylalanine may generally be classified as lower chain alkyl, aryl, or arylalkyl moieties. Derivatives of amino acid side chain moieties include other straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl or arylalkyl moieties.

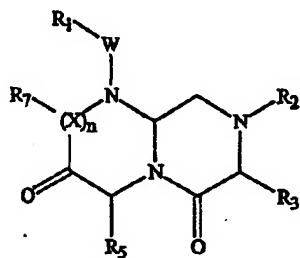
As used herein, "lower chain alkyl moieties" contain from 1-12 carbon atoms, "lower chain aryl moieties" contain from 6-12 carbon atoms and "lower chain arylalkyl moieties" contain from 7-12 carbon atoms. Thus, in one embodiment, the amino acid side chain derivative is selected from a C₁₋₁₂ alkyl, a C₆₋₁₂ aryl and a C₇₋₁₂ arylalkyl, and in a more preferred embodiment, from a C₁, alkyl, a C₆₋₁₀ aryl and a C₇₋₁₁ arylalkyl.

Amino side chain derivatives of this invention further include substituted derivatives of lower chain alkyl, aryl, and arylalkyl moieties, wherein the substituent is selected from (but are not limited to) one or more of the following chemical moieties: -OH, -OR, -COOH, -COOR, -CONH₂, -NH₂, -NHR, -NRR, -SH, -SR, -SO₂R, -SO₂H, -

SOR and halogen (including F, Cl, Br and I), wherein each occurrence of R is independently selected from straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl and aralkyl moieties. Moreover, cyclic lower chain alkyl, aryl and arylalkyl moieties of this invention include naphthalene, as well as heterocyclic compounds such as thiophene, pyrrole, furan, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, purine, quinoline, isoquinoline and carbazole. Amino acid side chain derivatives further include heteroalkyl derivatives of the alkyl portion of the lower chain alkyl and aralkyl moieties, including (but not limited to) alkyl and aralkyl phosphonates and silanes.

Representative R₁, R₂, R₃, R₄, R₅, R₆ and R₇ moieties specifically include (but are not limited to) -OH, -OR, -COR, -COOR, -CONH₂, -CONR, -CONRR, -NH₂, -NHR, -NRR, -SO₂R and -COSR, wherein each occurrence of R is as defined above.

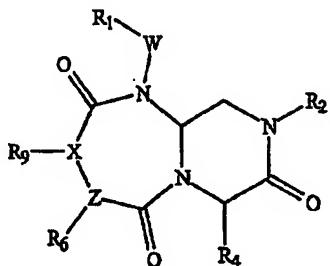
In a further embodiment, and in addition to being an amino acid side chain moiety or derivative thereof (or the remainder of the compound in the case of R₁, R₂, R₃, R₄, R₅, R₆ and R₇), R₁, R₂, R₃, R₄, R₅, R₆ or R₇ may be a linker facilitating the linkage of the compound to another moiety or compound. For example, the compounds of this invention may be linked to one or more known compounds, such as biotin, for use in diagnostic or screening assay. Furthermore, R₁, R₂, R₃, R₄, R₅, R₆ or R₇ may be a linker joining the compound to a solid support (such as a support used in solid phase peptide synthesis) or alternatively, may be the support itself. In this embodiment, linkage to another moiety or compound, or to a solid support, is preferable at the R₁, R₂, R₇ or R₆ position, and more preferably at the R₁ or R₂ position. In the embodiment wherein A is -(CHR₃), B is -(C=O)-, D is -(CHR₃), E is -(C=O)-, G is -(XR₇)_n-, the reverse turn mimetic compound of this invention have the following structure (I'):



wherein R₁, R₂, R₃, R₅, R₇, W, X and n are as defined above. In a preferred embodiment, R₁, R₂ and R₇ represent the remainder of the compound, and R₃ or R₅ is selected from an amino acid side chain moiety.

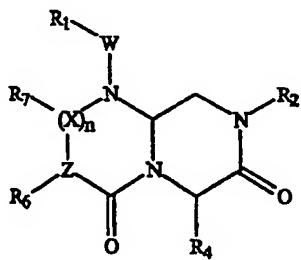
In the embodiment wherein A is -(C=O)-, B is -(CHR₃)-, D is -(C=O)-, E is -

(ZR₆)-, G is -(C=O)-(XR₉)-, the reverse turn mimetic compound of this invention have the following general structure (I'):



wherein R₁, R₂, R₄, R₆, R₉, W and X are as defined above, Z is nitrogen or CH (when Z is CH, then X is nitrogen). In a preferred embodiment, R₁, R₂, R₆ and R₉ represent the remainder of the compound, and R₄ is selected from an amino acid side chain moiety.

In a more specific embodiment wherein A is -(C=O)-, B is -(CHR₉)-, D is -(C=O)-, E is -(ZR₆)-, G is (XR₉)-, the reverse turn mimetic compound of this invention have the following structure (I''):

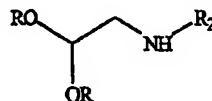


wherein R₁, R₂, R₄, R₆, R₇, W, X and n are as defined above, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero). In a preferred embodiment, R₁, R₂, R₆ and R₇ represent the remainder of the compound, and R₄ is selected from an amino acid side chain moiety. In this case, R₆ or R₇ may be selected from an amino acid side chain moiety when Z and X are CH, respectively.

The reverse-turn mimetic structures of the present invention may be prepared by utilizing appropriate starting component molecules (hereinafter referred to as "component pieces"). Briefly, in the synthesis of reverse-turn mimetic structures having structure (I), first and second component pieces are coupled to form a combined first-second intermediate, if necessary, third and/or fourth component pieces are coupled to form a combined third-fourth intermediate (or, if commercially available, a single

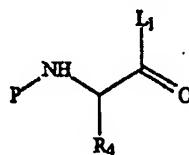
third intermediate may be used), the combined first-second intermediate and third-fourth intermediate (or third intermediate) are then coupled to provide a first-second-third-fourth intermediate (or first-second-third intermediate) which is cyclized to yield the reverse-turn mimetic structures of this invention. Alternatively, the reverse-turn mimetic structures of structure (I') may be prepared by sequential coupling of the individual component pieces either stepwise in solution or by solid phase synthesis as commonly practiced in solid phase peptide synthesis.

Within the context of the present invention, a "first component piece" has the following structure 1:



wherein R_2 as defined above, and R is a protective group suitable for use in peptide synthesis. Suitable R groups include alkyl groups and, in a preferred embodiment, R is a methyl group. Such first component pieces may be readily synthesized by reductive amination by displacement from $CH(OR)_2-CH_2-Hal$ (wherein Hal means a halogen atom) H_2N-R_2 .

A "second component piece" of this invention has the following structure 2:

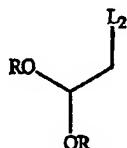


where L is carboxyl-activation group such as halogen atom, R_4 is as defined above, and P is an amino protective group suitable for use in peptide synthesis. Preferred protective groups include *t*-butyl dimethylsilyl (TBDMS), BOC, FMOC, and Alloc(allyloxycarbonyl). When L is $-C(O)NHR$, $-NHR$ may be an carboxyl protective group. N-Protected amino acids are commercially available. For example, FMOC amino acids are available from a variety of sources. The conversion of these compounds to the second component pieces of this invention may be readily achieved by activation of the carboxylic acid group of the N-protected amino acid. Suitable activated carboxylic acid groups include acid halides where X is a halide such as chloride or bromide, acid anhydrides where X is an acyl group such as acetyl, reactive esters such as an N-hydroxysuccinimide esters and pentafluorophenyl esters, and other activated intermediates such as the active intermediate formed in a coupling reaction using a

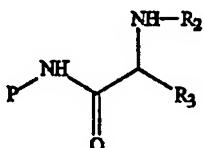
carbodiimide such as dicyclohexylcarbodiimide (DCC).

In the case of the azido derivative of an amino acid serving as the second component piece, such compounds may be prepared from the corresponding amino acid by the reaction disclosed by Zaloom et al. (*J. Org. Chem.* 46:5173-76, 1981).

Alternatively, the first piece of the invention may have the following structure

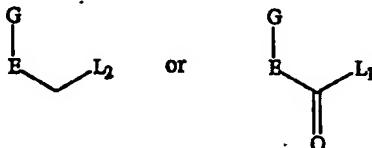


wherein R is as defined above and L₂ is a leaving group such as halogen atom or tosyl group, and the second piece of the invention may have the following structure 2':



wherein R_2 , R_3 and P are as defined above,

3b: A "third component piece" of this invention has the following structure 3a or

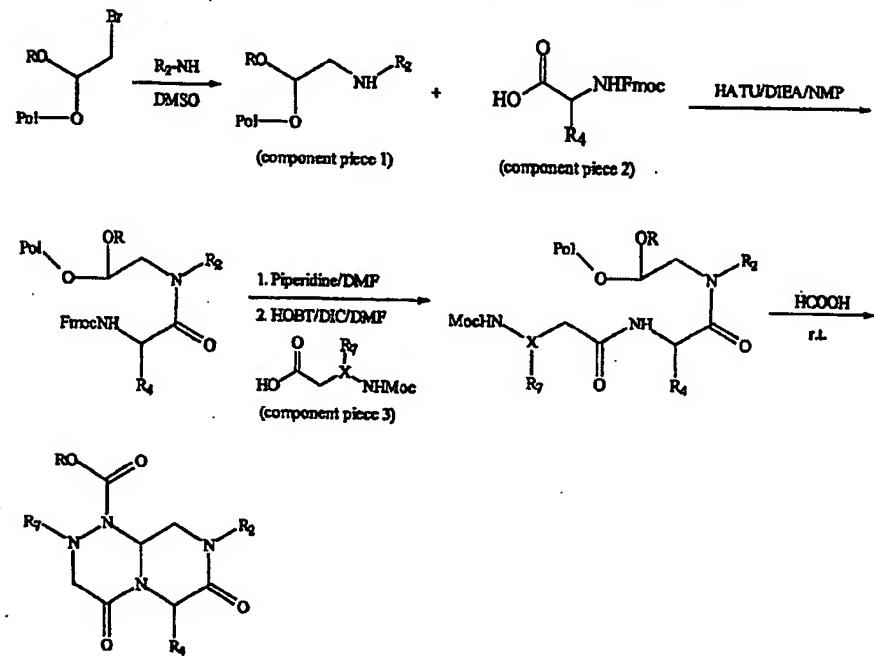


where G , E , L_1 and L_2 are as defined above. Suitable third component pieces are commercially available from a variety of sources or can be prepared by any known method in organic chemistry.

More specifically, the reverse-turn mimetic structures of this invention of structure (I) are synthesized by reacting a first component piece with a second component piece to yield a combined first-second intermediate, followed by either reacting the combined first-second intermediate with third component pieces sequentially to provide a combined first-second-third-fourth intermediate, and then cyclizing this intermediate to yield the reverse-turn mimetic structure.

The general synthesis of a reverse-turn having structure I' may be synthesized

by the following technique. A first component piece 1 is coupled with a second component piece 2 by using coupling reagent such as phosgene to yield, after N-deprotection, a combined first-second intermediate 1-2 as illustrated below:



wherein, R, R₂, R₄, R7, Fmoc, Moc and X are as defined above, and Pol represents a polymeric support.

The syntheses of representative component pieces of this invention are described in Example 1.

The reverse-turn mimetic structures of structures (I") through (I'') may be made by techniques analogous to the modular component synthesis disclosed above, but with appropriate modifications to the component pieces.

As mentioned above, the reverse-turn mimetics of USP 6,013,458 to Kahn are useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents. The opiate receptor binding activity of representative reverse-turn mimetics is presented in Example 9 of said USP 6,013,458, wherein the reverse-turn mimetics of this invention were found to effectively inhibit the binding of a radiolabeled enkephalin derivative to the δ and μ opiate receptors, of which data demonstrates the utility of these reverse-turn mimetics as receptor agonists and as potential analgesic agents.

The reverse-turn mimetic structures of the present invention will be useful as

bioactive agents, such as diagnostic, prophylactic, and therapeutic agents.

Therefore, since the compounds according to the present invention are of reverse-turn mimetic structures, it may be useful for modulating a cell signaling transcription factor related peptides in a warm-blooded animal, comprising administering to the animal an effective amount of the compound of formula (I).

Further, the reverse-turn mimetic structures of the present invention may also be effective for inhibiting peptide binding to PTB domains in a warm-blooded animal; for modulating G protein coupled receptor (GPCR) and ion channel in a warm-blooded animal; for modulating cytokines in a warm-blooded animal.

In another aspect of this invention, libraries containing reverse-turn mimetic structures of the present invention are disclosed. Once assembled, the libraries of the present invention may be screened to identify individual members having bioactivity. Such screening of the libraries for bioactive members may involve; for example, evaluating the binding activity of the members of the library or evaluating the effect the library members have on a functional assay. Screening is normally accomplished by contacting the library members (or a subset of library members) with a target of interest, such as, for example, an antibody, enzyme, receptor or cell line. Library members, which are capable of interacting with the target of interest, are referred to herein as "bioactive library members" or "bioactive mimetics". For example, a bioactive mimetic may be a library member which is capable of binding to an antibody or receptor, which is capable of inhibiting an enzyme, or which is capable of eliciting or antagonizing a functional response associated, for example, with a cell line. In other words, the screening of the libraries of the present invention determines which library members are capable of interacting with one or more biological targets of interest. Furthermore, when interaction does occur, the bioactive mimetic (or mimetics) may then be identified from the library members. The identification of a single (or limited number) of bioactive mimetic(s) from the library yields reverse-turn mimetic structures which are themselves biologically active, and thus useful as diagnostic, prophylactic or therapeutic agents, and may further be used to significantly advance identification of lead compounds in these fields.

Synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, in combination with the first, second and third component pieces of this invention. More specifically, any amino acid sequence may be added to the N-terminal and/or C-terminal of the conformationally constrained reverse-turn mimetic. To this end, the mimetics may be synthesized on a

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solid support (such as PAM resin) by known techniques (see, e.g., John M. Stewart and Janis D. Young, *Solid Phase Peptide Synthesis*, 1984, Pierce Chemical Comp., Rockford, Ill.) or on a silyl-linked resin by alcohol attachment (see Randolph et al., *J. Am Chem. Soc.* 117:5712-14, 1995).

In addition, a combination of both solution and solid phase synthesis techniques may be utilized to synthesize the peptide mimetics of this invention. For example, a solid support may be utilized to synthesize the linear peptide sequence up to the point that the conformationally constrained reverse-turn is added to the sequence. A suitable conformationally constrained reverse-turn mimetic structures which has been previously synthesized by solution synthesis techniques may then be added as the next "amino acid" to the solid phase synthesis (i.e., the conformationally constrained reverse-turn mimetic, which has both an N-terminus and a C-terminus, may be utilized as the next amino acid to be added to the linear peptide). Upon incorporation of the conformationally constrained reverse-turn mimetic structures into the sequence, additional amino acids may then be added to complete the peptide bound to the solid support. Alternatively, the linear N-terminus and C-terminus protected peptide sequences may be synthesized on a solid support, removed from the support, and then coupled to the conformationally constrained reverse-turn mimetic structures in solution using known solution coupling techniques.

In another aspect of this invention, methods for constructing the libraries are disclosed. Traditional combinatorial chemistry techniques (see, e.g., Gallop et al., *J. Med. Chem.* 37:1233-1251, 1994) permit a vast number of compounds to be rapidly prepared by the sequential combination of reagents to a basic molecular scaffold. Combinatorial techniques have been used to construct peptide libraries derived from the naturally occurring amino acids. For example, by taking 20 mixtures of 20 suitably protected and different amino acids and coupling each with one of the 20 amino acids, a library of 400 (i.e., 20^2) dipeptides is created. Repeating the procedure seven times results in the preparation of a peptide library comprised of about 26 billion (i.e., 20^8) octapeptides.

In a further aspect of this invention, methods for screening the libraries for bioactivity and isolating bioactive library members are disclosed. The libraries of the present invention may be screened for bioactivity by a variety of techniques and methods. Generally, the screening assay may be performed by (1) contacting a library with a biological target of interest, such as a receptor, and allowing binding to occur between the mimetics of the library and the target, and (2) detecting the binding event by an appropriate assay, such as by the calorimetric assay disclosed by Lam et al.

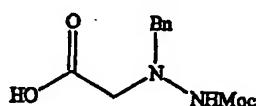
(*Nature* 354:82-84, 1991) or Grimsinski et al. (*Biotechnology* 12:1008-1011, 1994) (both of which are incorporated herein by reference). In a preferred embodiment, the library members are in solution and the target is immobilized on a solid phase. Alternatively, the library may be immobilized on a solid phase and may be probed by contacting it with the target in solution.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

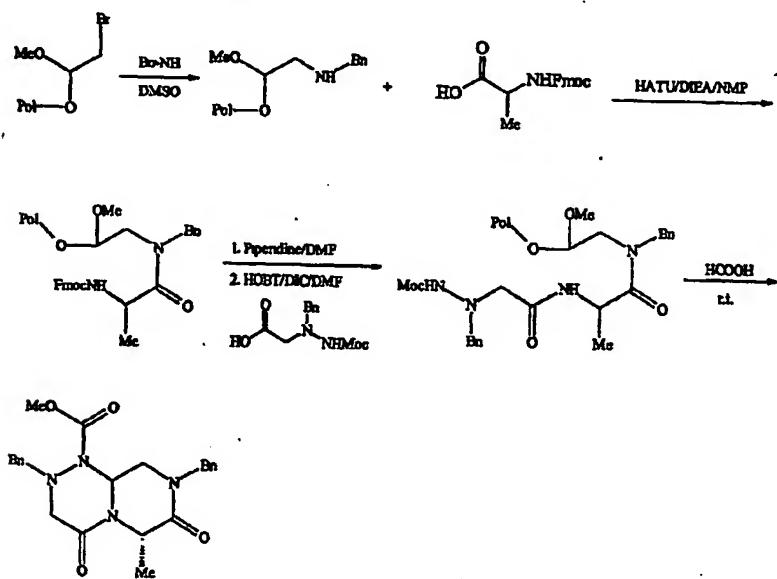
Example 1

(1) Preparation of *N*²-Moc-*N*⁶-benzyl-hydrazinoglycine



This compound was prepared according to literature procedure. (Cheguillaume et. al., *Synlett* 2000, 3, 331)

(2) Preparation of 1-Methoxycarbonyl-2,8-dibenzyl-6-methyl-4,7-dioxo-hexahydro-pyrazino[2,1-c][1,2,4]triazine



The bromoacetal resin (60 mg, 0.98 mmol/g) and a solution of benzyl amine in DMSO (2.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 h. The resin was collected by filtration, and washed with DMF, then DCM.

A solution of Fmoc-alanine (4 equiv.), HATU [PerSeptive Biosystems] (4 equiv.), and DIBA (4 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 h at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DME.

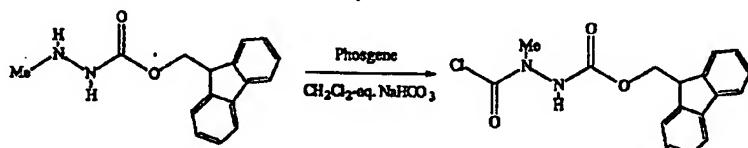
A solution of *N*²-Moc-*N*²-benzyl-hydrazinoglycine (4 equiv.), HOBT [Advanced ChemTech] (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin prepared above. After the reaction mixture was shaken for 3 h at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature.

The resin was treated with formic acid (2.5 ml) for 18 h at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

¹H NMR (400 MHz, CDCl₃) δ ppm; 1.51 (d, 3H), 2.99 (m, 1H), 3.39 (d, 1H), 3.69 (m, 1H), 3.75 (m, 1H), 3.82 (s, 3H), 4.02 (d, 1H), 4.24 (d, 1H), 4.39 (d, 1H), 4.75 (d, 1H), 5.14 (q, 1H), 5.58 (dd, 1H), 7.10-7.38 (m, 10H).

Example 2

(1) Preparation of *N*¹-Fmoc-*N*²-methyl-hydrazinocarbonyl chloride

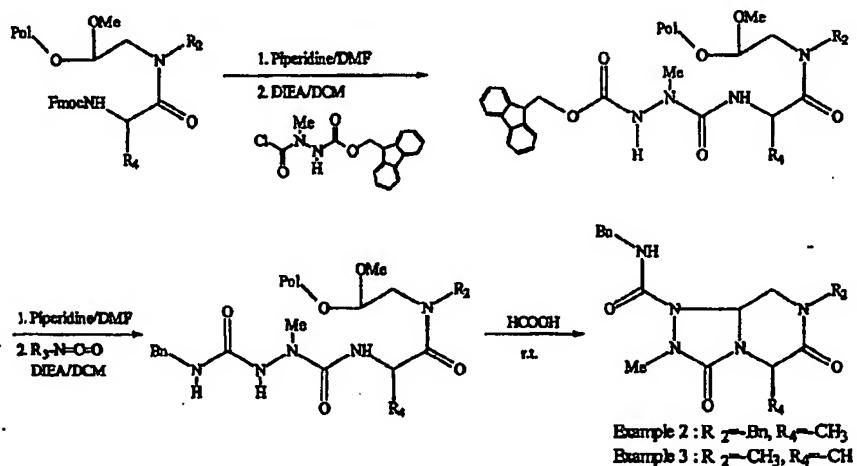


An ice-cooled biphasic mixture of N-Methyl hydrazine carboxylic acid 9H-Fluoren-9-ylmethyl ester (107 mg, 0.4 mmol) in 15 ml of CH₂Cl₂ and 15 ml of saturated aq. NaHCO₃ was rapidly stirred while a 1.93 M phosgene in toluene (1.03 ml, 2 mmol) was added as a single portion. The reaction mixture was stirred for 30 min, the organic phase was collected, and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced

pressure to afford 128 mg (97 %) of carbamoyl chloride as a foamy solid. [Caution: Phosgene vapor is highly toxic-use hood] This product was used for the following solid phase synthesis without further purification.

(2) Preparation of 2,5-Dimethyl-7-benzyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide

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The bromoacetal resin (30 mg, 0.98 mmol/g) and a solution of benzyl amine in DMSO (1.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 h. The resin was collected by filtration, and washed with DMF, then DCM.

A solution of Fmoc-alanine (3 equiv.), HATU [PerSeptive Biosystems] (3 equiv.), and DIEA (3 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 h at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

A solution of *N*²-Fmoc-*N*¹-methyl-hydrazinocarbonyl chloride (5 equiv.) obtained in the above step (1), DIEA (5 equiv.) in DCM was added to the resin prepared above. After the reaction mixture was shaken for 4 h at room temperature, the resin was collected by filtration and washed with DMF, DCM, and DMF.

To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin).

After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

The resin was treated with a mixture of benzyl isocyanate (4 equiv.) and DIEA (4 equiv.) in DCM for 4 h at room temperature. Then, the resin was collected by filtration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature.

The resin was treated with formic acid for 14 h at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

¹H NMR (400 MHz, CDCl₃) δ ppm; 1.48 (d, 3H), 2.98 (s, 3H), 3.18 (m, 1H), 3.46 (m, 1H), 4.37-4.74 (m, 5H), 5.66 (dd, 1H), 6.18 (m, 1H), 7.10-7.40 (m, 10H).

Example 3: Preparation of 2,5,7-Trimethyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide

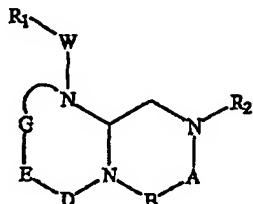
The title compound is prepared according to the same procedure with Example 2.

¹H NMR (400 MHz, CDCl₃) δ ppm; 1.48 (d, 3H), 2.99 (s, 3H), 3.03 (s, 3H), 3.38 (m, 1H), 3.53 (dd, 1H), 4.36 (dd, 1H), 4.52 (q, 1H), 4.59 (dd, 1H), 5.72 (dd, 1H), 6.19 (br.t, 1H), 7.10-7.38 (m, 5H).

It will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except by the appended claims.

We claim:

1. A compound having the following general structure (I):

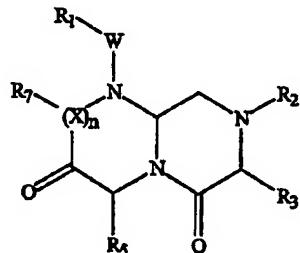


wherein A is $-(CHR_5)-$ or $-(C=O)-$, B is $-(CHR_4)-$, $-(C=O)-$, D is $-(CHR_3)-$ or $-(C=O)-$, E is $-(ZR_6)-$, $-(C=O)-$, G is $-(XR_7)_n$, $-(CHR_7)-(NR_8)_n$, $-(C=O)-(XR_9)-$, or $-(C=O)-$, W is $-Y(C=O)-$, $-(C=O)NH-$, $-(SO_2)-$ or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

2. The compound of claim 1, wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from the group consisting of aminoC₂₋₅alkyl, guanidinoC₂₋₅alkyl, C₁₋₄alkylguanidinoC₂₋₅alkyl, diC₁₋₄alkylguanidino-C₂₋₅alkyl, amidinoC₂₋₅alkyl, C₁₋₄alkylamidinoC₂₋₅alkyl, diC₁₋₄alkylamidinoC₂₋₅alkyl, C₁₋₃alkoxy, Phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C₁₋₄alkylamino, C₁₋₄dialkylamino, halogen, perfluoro C₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C₁₋₄alkylamino, C₁₋₄dialkylamino, halogen, perfluoro C₁₋₄alkyl, C₁₋₃alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C₁₋₄alkylamino, C₁₋₄dialkylamino, halogen, perfluoro C₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C₁₋₄alkylamino, C₁₋₄dialkylamino, halogen, perfluoro C₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridyl, substituted pyridyl, (where the substituents are

independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridyl C_{1-4} alkyl, substituted pyridyl C_{1-4} alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyrimidyl C_{1-4} alkyl, substituted pyrimidyl C_{1-4} alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy or nitro, carboxy, cyano, sulfuryl, or hydroxyl), triazin-2-yl- C_{1-4} alkyl, substituted triazin-2-yl- C_{1-4} alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazo C_{1-4} alkyl, substituted imidazol C₁₋₄alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, halogen, perfluoro C_{1-4} alkyl, C_{1-4} alkyl, C_{1-3} alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazolinyl C_{1-4} alkyl, N-amidinopiperazinyl-N- C_{0-2} alkyl, hydroxy C_{2-5} alkyl, C_{1-5} alkylamino C_{2-5} alkyl, hydroxy C_{2-3} alkyl, C_{1-5} alkylamino C_{2-3} alkyl, C_{1-5} dialkylamino C_{2-3} alkyl, N-amidinopiperidinyl C_{1-4} alkyl and 4-aminocyclohexyl C_{0-2} alkyl;

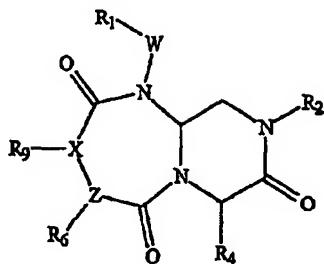
3. The compound of claim 1 wherein A is $-(CH_2)_3-$, B is $-(C=O)-$, D is $-(CH_2)_3-$, E is $-(C=O)-$, G is $-(XR_5)_n-$, and the compound has the following general structure (I):



wherein R₁, R₂, R₃, R₅, R₇, W, X and n are as defined in claim 1.

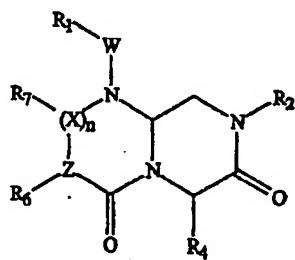
4. The compound of claim 1 wherein A is $-(C=O)-$, B is $-(CH_2)_4-$, D is $-(CH_2)_3-$

(C=O)-, E is -(ZR₆)-, G is -(C=O)-(XR₇)-, and the compound has the following general structure (I''):



wherein R₁, R₂, R₄, R₆, R₉, W and X are as defined in claim 1, Z is nitrogen or CH (when Z is CH, then X is nitrogen).

5. The compound of claim 1 wherein A is -(C=O)-, B is -(CHR₄)-, D is -(C=O)-, E is -(ZR₆)-, G is (XR₇)_n-, and the compound has the following general structure (I''):



wherein R₁, R₂, R₄, R₆, R₉, W, X and n are as defined in claim 1, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero).

6. The compound of any one of claims 2, 3 and 4, wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ or R₉ is joined to a solid support or solid support derivatives.

7. A library of compounds, comprising at least one compound of any one of claims 1 through 5

8. A pharmaceutical composition comprising a compound of claim 1 and pharmaceutically acceptable carrier.

9. A method of identifying a biologically active compound, comprising contacting the library of claim 8 with a target to detect or screen the biologically active compound.

00000000000000000000000000000000

ABSTRACT

Conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins are disclosed. Such reverse-turn mimetic structures have utility over a wide range of fields, including use as diagnostic and therapeutic agents. Libraries containing the reverse-turn mimetic structures of this invention are also disclosed as well as methods for screening the same to identify biologically active members.

002007-047660

DECLARATION AND POWER OF ATTORNEY

Attorney Docket No.: 37058-0008
Serial No.: not assigned

As the below named inventors, we hereby declare that:

Our residence and post office addresses and our citizenships are as stated below next to our names.

We believe that we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled **REVERSE-TURN MIMETICS AND METHOD RELATING THERETO**, the specification of which is being filed in the USPTO herewith.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application and to patentability as defined in Title 37, Code of Federal Regulations §1.56.

We hereby claim foreign priority benefits under Title 35, United States Code §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed: None.

We hereby claim the benefit under Title 35, United States Code §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations §1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

We hereby declare under penalty of perjury under the laws of the United States of America that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1021014797660

DECLARATION AND POWER OF ATTORNEY

Attorney Docket No.: 37058-0008
Serial No.: not assigned

We hereby appoint the following attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith:

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Executed on the _____ day of _____, 20____

Inventor's Signature: _____

Residence: 10916 80th Place NE Kirkland, WA 98034

Post Office Address: (same as above)

Citizenship: USA

DECLARATION AND POWER OF ATTORNEY

Attorney Docket No.: 37058-0008
Serial No.: not assigned

Full name of Second and Joint Inventor: Masakatsu Eguchi

Executed on the _____ day of _____, 20_____

Inventor's Signature: _____

Residence: 636 129th Place NE, Bellevue, WA 98005

Post Office Address: (same as above)

Citizenship: USA

Full name of Third and Joint Inventor: Sung Hwan Moon

Executed on the _____ day of _____, 20_____

Inventor's Signature: _____

Residence: 410-101 LG Village, Keumkok-Dong, Kwonsun-Ku, Suwon-shi, Kyunggi-do 441-460, Korea

Post Office Address: (same as above)

Citizenship: Republic of Korea

Full name of Fourth and Joint Inventor: Jae Uk Chung

Executed on the _____ day of _____, 20_____

Inventor's Signature: _____

Residence: 2-305 Samhwan Apt, Guyum-Dong Kwonsun-Ku, Suwon-shi, Kyunggi-do 441-703, Korea

Post Office Address: (same as above)

Citizenship: Republic of Korea

DECLARATION AND POWER OF ATTORNEY

Attorney Docket No.: 37058-0008
Serial No.: not assigned

Full name of Fifth and Joint Inventor: Sung Chan Lee

Executed on the _____ day of _____, 20_____

Inventor's Signature: _____

Residence: 336-1501 Chugong 3rd Apt, 1083 Kwonsun-Dong Kwonsun-Kn, Suwonshi,
Kyunnggi-do 441-390 Korea

Post Office Address: (same as above)

Citizenship: Republic of Korea

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